SCIENTIFIC ABSTRACT

Hunter syndrome is a rare (1/100,000 births), lethal, X-linked disorder of glycosaminoglycan (GAG) metabolism resulting from defective iduronate-2-sulfatase (IDS) enzyme activity and the consequent systemic accumulation of heparan sulfate and dermatan sulfate within lysosomes. As a model for mucopolysaccharidosis (MPS) storage diseases, Hunter syndrome is associated with global pathophysiology which sometimes includes the central nervous system (CNS). Death usually results from obstructive respiratory disease and/or complex cardiac involvement. Patients with the "mild form" experience only the somatic disease and survive to age 30 - 40 years. Conventional therapy is symptomatic and limited to palliative procedures (eg, herniorrhaphy, tracheostomy) which have virtually no impact upon the ultimate lethality of the disease. Allogeneic bone marrow transplantation (BMT) for patients with MPS diseases has been shown to provide a continuous source of enzyme and produces metabolic correction in many tissues as evidenced by reduction of urinary GAG excretion, disappearance of lysosomal inclusions from the liver, and amelioration of respiratory disease. However, several factors limit the application of BMT including the high morbidity and mortality of the procedure, lack of histocompatible donors, and tremendous cost of treatment ($200,000 - $1,000,000/patient). These limitations now motivate exploration of gene therapy. Preclinical studies suggest that retroviral-mediated insertion and expression of the human IDS gene in hematopoietic cells will prove to be a feasible, safe, and efficacious means of treating patients with mild Hunter syndrome. This phase I/phase II trial will use the clinically-proven retroviral gene delivery system (ie, LXSN) to assess the therapeutic effect of expressing recombinant IDS in 4 patients (2 adults and 2 children) with the mild form of Hunter syndrome. Eligibility criteria will include clinical features, biochemical abnormalities, and identification of the specific gene mutation, to identify those individuals with genotypes characteristic of the mild form of Hunter syndrome. Peripheral blood lymphocytes (PBL) will be harvested by apheresis and then stimulated with anti-CD3 antibody and maintained in culture with IL-2 to expand T-lymphocyte populations. Utilizing L2SN (IND #5370, a therapeutic retroviral vector designed for insertion and expression of the IDS gene), PBL will be transduced ex vivo and then infused on a monthly basis. Subsequent studies will determine the frequency of PBL transduction and the half-life of infused cells. Evaluation of patients will include measurement of blood levels of the recombinant IDS enzyme, assessment of metabolic correction (ie, urinary GAG levels), clinical response of the disease (ie, liver and spleen volume, pulmonary function tests, echocardiography, EKG), and monitor for potential toxicities. Although patients with mild Hunter syndrome are characterized by normal intellect, this study will also assess GAG deposition in the CNS by magnetic resonance imaging. In summary, this phase I/phase II study is anticipated to demonstrate the safety of L2SN-mediated gene therapy and provide a preliminary evaluation of clinical efficacy.